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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,313	08/10/2001	Rudolph E. Tanzi	0609.4460004	7393

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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,313	TANZI ET AL.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/2002* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS: 8/2002* .

DETAILED ACTION

1. Currently, claims 33-43 are pending in the instant application. Claims 1-32 have been canceled in a preliminary amendment filed 8/10/2001.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example, see p. 36). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3. The amendment filed 8/10/2001 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the recitation of "blood" in claim 33 has introduced new matter into the specification. A thorough review of the paragraphs applicants provide in support of the newly added claims reveals that no reference to "blood" is present. Further, the claim as originally filed did not stipulate "blood" as a sample type. The specification teaches samples such as "cells tissues, or organs" in paragraph 38, however the specification does not recite "blood".

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 33-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide sufficient guidance to enable the skilled artisan to make and use the claimed Alzheimer's disease diagnosis method without undue experimentation because neither the specification nor the art predictably teach that the genotype of the α_2M-2 variant, let alone the presence of the protein α_2M-2 variant, is correlated to Alzheimer's disease. The claims are broadly drawn to a method of assessing whether and individual is at risk for developing AD or a method for use in diagnosis of AD, by isotyping a sample to determine whether the sample contains the α_2M-2 variant. The specification and Blacker et al (Nature Genetics, vol. 19, 357-360; 8/1998) teach that inheritance of the A2M-2 mutation (deletion of 5 base pairs at the 5' acceptor splice site of exon 18) conferred increase risk for Alzheimer's disease. However, further studies in the art contradict these results making the association between Alzheimer's disease and the A2M-2 gene polymorphism unpredictable. Specifically, Hu et al (Neurology, May 1999 vol. 53, pp 642-643) found no association between the A2M-2 mutation with Alzheimer's disease in a Taiwanese population. Furthermore, Crawford et al (Neuroscience Letters, August 1999, vol. 270, pp 133-136) conducted an investigation on clinic and community based samples in order to clarify the influence of the A2M-2 mutation on Alzheimer's disease and found no association between A2M and Alzheimer's disease.

As a result of these conflicting results, undue experimentation would be required of the skilled artisan to practice the claimed assessment and diagnosis methods because association of the α_2M-2 variant and AD has not been predictably established. Therefore, the skilled artisan would be required to conduct a large scale isotyping method without reasonable expectation that an association between the α_2M-2 variant and Alzheimer's disease exists. Such a method would consist mainly of trial and error analysis and is therefore considered undue.

6. Applicant NOTE: a declaration was submitted in parent application 09/148,503 and was found persuasive to overcome 112/first paragraph rejections in the '503 application. If such a declaration were filed in the instant application, it would be sufficient to overcome the 112/first paragraph rejection set forth above.

New Matter

7. Claims 33-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

The preliminary amendment filed 8/10/2003 and the recitation of "blood" in claim 33 has introduced new matter into the specification. A thorough review of the paragraphs applicants provide in support of the newly added claims reveals that no reference to "blood" is present. Further, the claim as originally filed did not stipulate "blood" as a sample type. The specification teaches samples such as "cells tissues, or organs" in paragraph 38, however the specification does not recite "blood".

Indefinite

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 33-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33 and 38 are indefinite as the claims lack a positive process step relating back to the preamble. The preamble of claim 33 recites "A method of assessing an individual's risk of developing AD" while the last positive step is to determine whether an individual contains the α_2M-2 variant. Therefore it is unclear if the method is to assess an individual's risk of developing AD or simply a method to determine if an individual has the α_2M-2 variant. The preamble of claim 38 states "a method used to aid in the diagnosis of AD", while the last positive step is to determine if a sample has the α_2M-2 variant, therefore it is unclear if the method is a method of diagnosis or simply a method to determine the presence of the α_2M-2 variant in a sample. In claim 38, the recitation of "used to aid" is also indefinite because it is unclear if the preamble is drawn to a diagnostic method or to a method of detecting a variant.

Claim 33 is indefinite in the recitation of "blood tissue or cell sample…" because it is unclear if a "," is missing between "blood" and "tissue". It appears that the claim intended "blood, tissue or cell".

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 33, 35-39 and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthjis et al (hereinafter referred to as Matthjis, Nucleic Acids Research, vol. 19, p s102, 1991) each in view of Justus et al (hereinafter referred to as Justus, Journal of Immunological Methods, vol. 126, pp 103-108, 1990) and Bauer et al (hereinafter referred to as Bauer, FEBS Letters, vol 285, pp 111-114, 1991).

The claim have been broadly interpreted to encompass a method using isotyping to determine the presence of the α_2M-2 variant. Matthjis teaches detection of the α_2M-2 variant nucleic acid in samples. Although Matthjis does not teach detection of the protein variant. Matthjis teaches determining the allele frequencies in different populations.

Justus teaches quantification of free α_2M and α_2M-protease complexes using ELISA.

Bauer et al teach methods of detecting α_2M in samples using immunohistochemistry, in patients with Alzheimer's disease. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine the frequency of the

α_2M-2 and α_2M-1 (wildtype) variants in different population as taught by Matthjis, using the immunochemical methods of Justus or Bauer for the purposes of providing a more complete assessment of the frequency of α_2M-2 alleles in different populations. The ordinary artisan would further have been motivated to determine the allele frequencies as taught by Matthjis with the immunochemical methods of either Justus or Bauer because doing so would have provided an easy alternative approach to nucleic acid based methods. Although neither Justus nor Bauer teach an antibody specific for the α_2M-2 variant, as the nucleic acid and protein sequence of the α_2M-2 variant were known in the art at the time of the invention, it would have been well within the skill of the ordinary artisan at the time the invention was made, to construct antibodies specific for the α_2M-2 variant. It is noted that the claims have been interpreted to only encompass detection of the α_2M-2 variant, that is, the diagnosis and assessment methods of the preamble have not been given weight as the last positive process step, relating detection of the variant to AD is missing in the rejected claims. Claims that recite such steps, such as claims 34 and 40, have not been rejected.

Conclusion

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Primary Examiner
Art Unit 1634
9/2/03